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CHAPTER 33

Bladder Cancer, Tap Water Consumption, and Drinking Water Source

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INTRODUCTION

In the proceedings of the previous (fifth) conference on water chlorination, we presented results of initial analyses of water source and treatment effects on bladder cancer risk from a large population-based case-control interview study.[1] Our findings were that bladder cancer risk in the full study population was not associated with duration of exposure to chlorinated surface water. However, among nonsmokers never employed in a high-risk occupation, a group otherwise at low risk, we found that bladder cancer risk was associated with the number of years at a residence served by chlorinated surface waters, with the risk ratio increasing to 2.3 after 60+ years of exposure (relative to lifetime nonchlorinated groundwater users).

The earlier analyses did not include information from study subjects on their consumption of tap water and beverages made with tap water. In subsequent analyses, reported here, we have included this information. The current findings extend our previous observations and suggest that chlorination byproducts, or other contaminants common to most disinfected surface waters, are risk factors for bladder cancer. For convenience, we include a description of the study design before describing our updated findings and their limitations and possible implications.

STUDY METHODS

The National Bladder Cancer Study was conducted by the National Cancer Institute in collaboration with the Food and Drug Administration, the U.S. Environmental Protection Agency (EPA), and ten collaborating centers. Eligible cases included all persons aged 21 to 84 diagnosed with cancer of the urinary bladder in 1978 and residing in ten areas of the United States (Connecticut, Iowa, New Jersey, New Mexico, and Utah and metropolitan Atlanta, Detroit, New Orleans, San Francisco, and Seattle). Slightly less than one-third of the cases were from New Jersey. Connecticut, Iowa, Detroit, and San Francisco each accounted for more than 10%. Bladder cancer is primarily a disease of older men. Three times as many cases were male as female, and the median age was 67. We interviewed 2982 cases, 73% of the eligible pool. Controls were randomly selected from the population of each area, frequency matching on sex, 5-year age group, and study area. Controls between 21 and 64 years of age were selected by a random-digit dialing method, and controls aged 65 to 84 were randomly selected from a roster provided by the Health Care Financing Agency; 5782 population-based controls were interviewed. Further details on study design and methods are available.[2]

Cases and controls were interviewed at home by trained interviewers. The questionnaire included demographic background; a smoking, occupation, and medical history; artificial sweetener use; and other possible risk factors such as hair dyes, coffee and tea consumption, tap water consumption, alcoholic beverage intake, and consumption of other beverages. Each respondent was asked to name each city or town of residence for one year or more, the years moved into and out of each place, and whether the primary source of drinking water at each place was a private well or spring, the community water supply, bottled water, or another source. We coded places of residence using a standard geographic coding scheme.

In collaboration with the Cincinnati Health Effects Research Laboratory of the EPA, we conducted an ancillary survey of over 1100 community water supplies that served more than 1000 persons each, in the ten study areas. We collected historical information on water source, treatment, and geographic distribution since 1900. Water sources were classified as surface, ground, or combined, with further details on potential sources of contamination. Information on treatment, especially chlorine disinfection, was also gathered. Although details on amounts of added chlorine were usually not available from utilities, we were able to ascertain the years in which chlorine disinfection had been used. The towns and cities historically served by each water source were listed and coded with the geocoding system used for residential histories. For each study subject, we created a year-by-year record of residential water source and treatment. For each year that a respondent lived in one of the ten study areas and used a community supply, we looked up water source and treatment information for the appropriate purveyor in the water supply data file. We were not able to describe the water source for the time periods when respondents used community sources outside of the study areas or when they lived in very small communities with supplies not covered by our survey. The year-by-year profile of water source and treatment information for each person provided us with a flexible tool to look at patterns of water use as well as to define individual exposures. We estimated relative risks according to several different measures of exposure. Our primary focus here is risk as a function of fluid intake, especially tap water, and as a function of duration of residence served by chlorinated surface water. Most chlorinated surface sources have much higher levels of chlorination by-products than most chlorinated or nonchlorinated groundwater sources.[3] This justified our using duration of chlorinated surface water use as one index of exposure.

We used the odds ratio to estimate relative risks. Logistic regression for unmatched data was used to obtain a maximum likelihood point and 95% confidence interval estimates of the odds ratio and to control for potential confounding of selected variables.[4] Among the potential confounders in most calculations were geographic area (ten levels); population size/urbanicity of the longest duration place of residence [three levels: <50,000, not in a standard metropolitan statistical area (SMSA); <50,000, within an SMSA; and 50,000+ (an SMSA)]; cigarette smoking intensity (six levels); age (three groups); employment in a high-risk occupation (defined as one that conferred a relative risk of 1.5+ in this study population); and sex when the analyses were not sex specific. The current analyses were restricted to white respondents, numbering 2805 cases and 5258 controls.

RESULTS

Bladder Cancer Risk and Fluid Intake

The first analyses evaluated risk associated with total beverage consumption, entered as a continuous variable (in units of liters/day) in logistic regression models. Logistic regression coefficients (units, liters/day) were 0.112 for men ($p < 0.0001$), 0.117 for women ($p = 0.07$), and 0.122 ($p < 0.001$) overall. The overall relative risk per daily liter increase in intake is the antilog of the regression coefficient, or about 1.13. In a subsequent analysis, total fluid consumption was separated into variables representing daily tap water intake (tap water per se, coffee, tea, appropriate fraction of reconstituted juices) and other beverage fluid intake (soft drinks, milk, beer, etc.). Among men, the coefficients for tap and nontap beverages were 0.176 ($p < 0.0001$) and 0.037 ($p = 0.42$) and among women, 0.123 ($p = 0.09$) and 0.089 ($p = 0.37$), respectively. This suggests that the risk associated with total beverage consumption was linked with its tap water component, but not with fluid from other sources.

Chlorinated surface waters contain both volatile and nonvolatile chlorination by-products. Volatiles are partially removed through boiling. When tap water was expressed as two continuous variables representing its "heated" (coffee and tea) and "nonheated" (water per se and reconstituted juices) components, the respective coefficients were 0.190 ($p < 0.001$) and 0.156 ($p < 0.001$). These results are consistent with an effect of nonvolatile contaminants from tap water that are present in both heated and nonheated beverages.

Risks by quintile of tap water consumption, relative to the lowest quintile (< 0.81 L/d) are shown in Table 1. The relative risk increased with daily intake, with a relative risk of 1.43 for the highest vs the lowest consumption quintile. The chi-square for trend was highly significant for both sexes combined and for men ($p < 0.0001$), but not for women. These results are consis-

Table 1. Relative risks (RR) and 95% confidence intervals (CI) for bladder cancer according to quintile of reported tap water consumption[a]

Tap water ingestion level (L/d)	No. of cases	No. of controls	RR	(95% CI)
≤0.80	446	1047	1.0	
0.81–1.12	505	1083	1.08	(0.93, 1.26)
1.13–1.44	520	1039	1.14	(0.98, 1.34)
1.45–1.95	582	991	1.32	(1.13, 1.54)
1.96+	642	921	1.43	(1.23, 1.67)
Chi-square (trend)		26.5		
p (trend)		<0.0001		

[a]From logistic regression, adjusted for sex, age, high-risk occupation, smoking level, population size of usual residence, and reporting center.

tent with findings from the logistic regression models using continuous variables. A more comprehensive description of these results is presented elsewhere.[5]

Risk by Duration of Chlorinated Surface Water Use and Tap Water Intake

Evaluation of bladder cancer risk by the combined effects of duration of chlorinated surface source use and tap water intake required restriction of the analyses to individuals with reliable information for both items. Water source for many respondents was incompletely characterized because they had lived outside of study areas or in very small places not covered by our water utility survey, or their water came from combined surface and ground sources. To minimize the influence of incomplete exposure information, subsequent analyses were restricted to cases and controls for whom the summed years at places uniquely served by either chlorinated surface sources or nonchlorinated ground sources accounted for more than 50% of their lifetime. After eliminating the remaining subjects, the reduced study population included 1225 male cases, 2223 male controls, 405 female cases, and 804 female controls representing 57.8% of the total study population. The 3027 controls eligible for inclusion were similar to excluded respondents with respect to sex, cigarette smoking levels, employment in high-risk occupations, and number of lower urinary tract infections. Risks for cigarette smoking, high-risk occupation, and tap water intake were similar among populations included in the analysis and those excluded.

Relative risks for bladder cancer were calculated by duration of residence at places with chlorinated surface sources. The low-exposure comparison group was persons who had never used surface water and whose customary source of water was a nonchlorinated spring or well. Among men, and overall, there was little increase in bladder cancer risk with increasing duration of surface water use. The risk for bladder cancer was 0.99 among men with 60+ years of use of chlorinated surface water, relative to men with no use. However, bladder cancer risk among women increased with duration of surface water use, with a significant trend (chi-square = 4.1, $p = 0.04$). Relative to women who never used chlorinated surface water, the risk was 1.5 for 1 to 19 years of use, 1.2 for 20 to 39 years, 1.5 for 40 to 59 years, and 2.1 (CI = 1.1,4.0) for 60+ years.

Table 2 shows relative risk for bladder cancer with increasing tap water intake level within strata grouped by duration of residence at places with a chlorinated surface source. Risk was not associated with intake among those with no or with 1 to 19 years of reported chlorinated surface water use. Small, nonsignificant increases in risk with tap water intake were found among persons with 20 to 39 years of exposure to chlorinated surface waters. Respondents with 40 to 59 or 60+ years of surface water use showed the strongest bladder cancer risk gradients with tap water intake. The relative risks were 1.7 and 2.0, respectively, for the highest vs lowest consumption quintile. The test for trend with intake was significant within these two longest-duration strata ($p = 0.006$ and 0.014). When analyzed by geographic region, risk increased with total tap water intake in eight of the ten study areas, with a statistically significant positive trend in three places (New Jersey, Detroit, and San Francisco). The trend was slightly negative (not significant) in two places (New Orleans and Iowa).

Relative risks for the combined effects of tap water ingestion level and duration of chlorinated surface water use are shown in Table 3. Risks are relative to persons who consumed <0.81 L daily and whose lifetime residences were at places served by nonchlorinated groundwater and never by chlorinated surface sources (43 cases, 108 controls). Gradients of increasing risk with duration of chlorinated surface sources were observed only among those in the upper two quintiles of tap water consumption. Similarly, increasing risk with level of tap water ingestion was found primarily among persons who lived at residences served by chlorinated surface water sources for at least 40 years.

We earlier reported an association between bladder cancer risk and duration of chlorinated surface water use among nonsmokers, but not among smokers.[1] This was consistent with the finding of an overall duration effect among women, but not men, given lower historical female smoking rates. Table 4 shows relative risks with increasing duration of exposure among nonsmokers by their level of tap water ingestion. Overall bladder cancer risk was more strongly associated with duration among high-level consumers (above the population median) than lower-level consumers. There were some inconsistencies in this measure when analyzed by sex, in that the gradient with duration among women was actually slightly stronger among those who consumed less tap water than the population median level. Among both female and male nonsmokers, the overall relative risk for 60+ years of exposure to chlorinated surface waters was 3.1 (CI = 1.3,7.3) relative to nonsmokers who had used

Table 2. Relative risks (RR) for bladder cancer according to quintile of reported tap water ingestion, by duration of residence served by a chlorinated surface water source[a]

Tap water ingestion level (L/d)	Years of residence with chlorinated surface water														
	0			1–19			20–39			40–59			60+		
	CA	Ct1	RR	CA	Ct1	RR	CA	Ct1	RR	CA	Ct1	RR	CA	Ct1	RR
≤0.80	43	108	1.0	32	60	1.0	71	133	1.0	95	238	1.0	26	53	1.0
0.81–1.12	55	133	1.0	33	63	1.0	80	186	0.8	126	206	1.6	23	58	0.8
1.13–1.44	54	129	1.2	39	62	1.2	69	152	0.8	107	198	1.3	28	51	1.1
1.45–1.95	49	156	0.8	35	64	0.9	94	142	1.2	125	174	1.7	28	33	1.7
1.96+	67	126	1.2	49	78	1.0	110	145	1.2	122	159	1.7	31	30	2.0
Chi-square (trend)		0.12			0.02			3.49			7.51			6.09	
p		0.73			0.89			0.06			0.006			0.014	

[a]From logistic regression, adjusted for sex, age, high-risk occupation, smoking level, population size of usual residence, and reporting center.

Table 3. Relative risks for bladder cancer according to combined tap water ingestion level and duration of chlorinated surface water source[a]

Ingestion level (L/d)	Years of residence with chlorinated surface water				
	0	1–19	20–39	40–59	60+
≤0.80	1.0 (43, 108)[a]	1.2 (32, 60)	1.1 (71, 133)	0.8 (95, 238)	1.0 (26, 53)
0.81–1.12	1.1 (55, 133)	1.0 (33, 63)	0.9 (80, 186)	1.3 (126, 206)	0.8 (23, 58)
1.13–1.44	1.1 (54, 129)	1.4 (39, 62)	0.9 (69, 152)	1.1 (107, 198)	1.0 (28, 51)
1.45–1.95	0.7 (49, 156)	1.1 (35, 64)	1.3 (94, 142)	1.3 (125, 174)	1.7 (28, 33)
1.96+	1.1 (67, 126)	1.1 (49, 78)	1.3 (110, 145)	1.4 (122, 159)	1.8 (31, 30)

[a]From logistic regression adjusted for sex, age, smoking habit, high-risk occupation, population size of usual place of residence, and reporting center.
[b]Values in parentheses refer to number of cases, number of controls.

Table 4. Relative risks among nonsmokers for bladder cancer according to duration of residence with a chlorinated surface source, by tap water ingestion level[a]

	Tap water intake							
	Below population median				Above population median			
Years	Ca	Ctl	RR	(95% CI)	Ca	Ctl	RR	(95% CI)
0	34	152	1.0		35	139	1.0	
1–19	23	71	1.5	(0.8, 3.0)	14	54	1.1	(0.5, 2.4)
20–39	41	142	1.2	(0.6, 2.4)	44	117	1.9	(1.0, 3.7)
40–59	70	239	1.1	(0.5, 2.2)	58	153	2.0	(1.0, 4.1)
60+	26	51	2.0	(0.9, 4.6)	27	36	3.1	(1.3, 7.3)
Chi-square (trend)			0.71				6.32	
p (trend)			0.40				0.01	

[a]From logistic regression adjusted for age, smoking habit, high-risk occupation, population size of usual residence, reporting center, and sex.

unchlorinated groundwater. The increase in risk with duration of chlorinated surface water use was highly significant.

SUMMARY AND CONCLUSIONS

These findings confirm and extend results of earlier studies that had reported associations for bladder cancer with consumption of chlorinated surface waters.[6,7] Relative risks in this study were generally low (in the range 1.2 to 2.0), giving some hesitancy to interpretation of results as showing causal associations. Risks of this magnitude could have been due to confounding from risk factors (or protective nutrients) that were not ascertained. The study was originally designed to measure risk associated with saccharin consumption, so study areas were not selected to maximize within-area variation in water supply, and five of the ten areas were metropolitan regions served predominantly by one water source. Throughout our analyses, we assumed that nonchlorinated groundwater sources were free of contamination. Our result may be biased toward the null to the extent that this was not true, and groundwater contaminants were bladder cancer risk factors. Respondents were asked about beverage consumption a year before the interview. Although respondent's reported tap water intake levels were consistent with findings from other surveys, increasing one's confidence in accuracy, we do not know how well reported levels of recent intake represented lifetime consumption patterns. Randomly inaccurate assessment of intake would have the effect of lowering estimates of risk, while differential over- or under-reporting between cases and controls could bias the estimates up or down.

These limitations notwithstanding, the findings for bladder cancer risk from the study are suggestive. Among the criteria for judgment in assessing causality from epidemiological findings are internal and external consistency, dose-response gradients, coherence, high relative risks, and biological plausibility.[8] Our findings meet these criteria except for not showing high relative risks. With minor exception, the results are similar for men and for women and are consistent among the geographic areas. Dose-response patterns, both with regard to tap water intake and exposure duration, would be difficult to explain by invoking the action of one or more confounding factors. Toxicological evaluations have demonstrated the genotoxicity and transforming activity of chlorination by-products in a variety of testing systems.[9] If the positive findings of the current study are not the spurious result of bias or confounding, they suggest that about 12% of bladder cancers in this study population were caused by surface water contaminants as calculated from results in Table 3.[10] Among nonsmokers, the attributable risk was about 27% (from data in Table 4). There is clearly a need to have the findings from this case-control study replicated by other investigators in different settings. Before confirmatory evidence is available, however, prudent public health practice would dictate that exposure to chlorination by-products be minimized, while ensuring disinfection adequate to remove infectious microbial and viral agents.

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